

# A new composite technique to estimate the input function for FDG-PET brain quantitative analysis without any blood sample

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**Abstract-** The quantitative determination of LCMRGlc (Local Cerebral Metabolic Rate of Glucose) is one of the advantages for FDG-PET ( $[^{18}\text{F}]2\text{-fluoro-2-deoxy-D-glucose}$  positron emission tomography) in diagnosis of brain functions. However, in the FDG 3-compartment model, an input function made of arterial blood samples is necessary for the computation. Due to the invasion of arterial lines and inconvenience of the sampling schedule, FDG quantitative analysis is seldom performed in practice. To solve this dilemma, some methods have been used to simplify the sampling schedule. But one or two blood samples are still needed, or the estimated LCMRGlc may be seriously biased. This paper proposes a new composite technique based on two current methods to estimate the input function without any blood sample. Eighteen patients are tested with this new approach, together with current methods for evaluation. The results show that this new technique can provide reliable estimation of the input function, and the bias of K constants is also reduced when the estimated input function is used.

**Keywords** - input function, non-invasive, blood samples, quantitative, FDG

## I. INTRODUCTION

Although PET (positron emission tomography) can provide a functional view in the diagnosis of brain disorders, its low resolution and signal-to-noise ratio will cause that the visual interpretation highly relies on personal experience. Model analysis using PET images can provide the true quantitative information of brain functions; such as glucose metabolic rate and cerebral blood flow in an objective way.

Among many kinds of the available tracers, this paper focuses on the tracer FDG ( $[^{18}\text{F}]2\text{-fluoro-2-deoxy-D-glucose}$ ), an analogue of glucose in PET. The 3-compartment FDG model as shown in Fig.1 was developed by Sokoloff et al. [1] and further extended by Huang et al. [2]. The input function, denoted as  $c_p^*(t)$ , is obtained from arterial blood samples. To avoid the risk of arterial insertion, about 20 arterialized venous samples are used as an alternative to construct  $c_p^*(t)$ . Due to the invasion of arterial lines and inconvenience of the sampling schedule, several methods have been proposed to obtain the input function by fewer samples. For methods based on less than two samples, two major approaches have been developed. Takikawa et al. proposed a “population-based” arterial blood curve, using statistical analysis to establish the model for constructing the blood curve by one or two blood samples [3]. With the same statistical idea, Wakita et al. also established a 1-point blood-sampling schedule, based on the statistical analysis of 120 patients [4]. For the second approach, Feng et al. proposed the simultaneous estimation (SIME) method [5], where the input function can be estimated simultaneously with the k parameters with three or more regions of interest (ROIs).

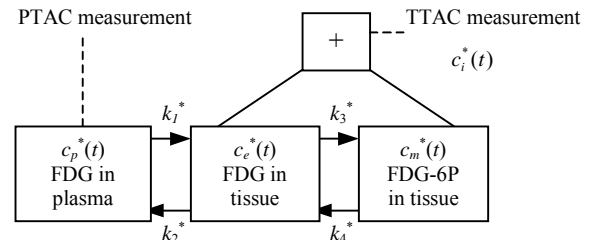


Fig. 1. FDG 3-compartment model

The advantage of SIME is the ability to estimate the input function without any blood sample. However, to recover the input function by 3-ROI SIME, a total number of  $6+(5 \times 3)=21$  parameters have to be estimated. Apparently, large amount of computation would be required, and the result might be biased because each parameter can only be varied within a relatively narrow range. In this paper, we propose the SSIME (Simplified Simultaneous Estimation) method based on SIME and 1-point blood-sampling method. Similar to the SIME method, multiple ROIs are used to estimate the input function, but the input function model is replaced by the 1-point blood-sampling method of Wakita et al., which depends only on one parameter (the blood sample at the 40th minute). According to the experiment results, a better estimated input function, which is closer to the real blood curve, could be obtained.

## II. METHODOLOGY

### Data Acquisition

Eighteen patients were collected in this study. Data were acquired with the GE/Scanditronix PC4096WB PET scanner in National PET/Cyclotron Center, Taipei Veterans General Hospital. For each patient, a real plasma time-activity curve (PTAC) was measured at times of 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6.5, 10, 15, 20, 30, 60, 90, and 120 minutes after injection. After iv injection of 10 mCi of FDG, a two hour dynamic data acquisition was started in the following sequence: 10x 12-sec frames, 2x 30-sec frames, 2x 1-min frames, and 3x 30-min frames [6]. To prepare for the parameter estimation, ten ROIs are circled at the same locations for each patient as illustrated in Fig. 2. Parameters are estimated by non-linear least squares, and MATLAB version 5.3 is used as the developing environment.

### FDG kinetic model

The solution of the 3-compartment FDG model as shown in Fig.1 can be obtained by Laplace transform. The relation between tissue time-activity curve (TTAC)  $c_i^*(t)$  and PTAC  $c_p^*(t)$  is:

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$$c_i^*(t) = (B_1 e^{-L_1 t} + B_2 e^{-L_2 t}) \otimes c_p^*(t), \quad (2)$$

where

$$B_1 = \frac{k_1^*}{(\alpha_1 - \alpha_2)} \{k_3^* + k_4^* - \alpha_1\}, L_1 = \frac{1}{2} \{(k_2^* + k_3^* + k_4^*) - \sqrt{(k_2^* + k_3^* + k_4^*)^2 - 4k_2^* k_4^*}\},$$

$$B_2 = \frac{k_1^*}{(\alpha_1 - \alpha_2)} \{\alpha_2 - k_3^* - k_4^*\}, L_2 = \frac{1}{2} \{(k_2^* + k_3^* + k_4^*) + \sqrt{(k_2^* + k_3^* + k_4^*)^2 - 4k_2^* k_4^*}\}$$

When a ROI is circled in certain area of the brain, one TTAC can be generated from PET dynamic data. With the PTAC measured from arterial samples or arterialized venous samples, NLLS (non-linear least squares) with the Newton-Gaussian or Levenberg-Marquardt algorithm can be used for estimation of  $B_1$ ,  $B_2$ ,  $L_1$  and  $L_2$ .  $k_1$ - $k_4$  can then be calculated by:

$$k_1^* = B_1 + B_2, k_2^* = \frac{B_1 L_1 + B_2 L_2}{B_1 + B_2}, k_4^* = \frac{L_1 L_2 (B_1 + B_2)}{B_1 L_1 + B_2 L_2}, k_3^* = \frac{B_1 L_2 + B_2 L_1}{B_1 + B_2} - k_4^*$$

The LCMRGlc is calculated by:

$$R_i = \frac{1}{LC} \frac{k_1^* k_3^*}{k_2^* + k_3^*} c_p \equiv \frac{1}{LC} K c_p \quad (3)$$

where LC is the lumped constant,  $c_p$  is the “cold” concentration of glucose in blood, and  $K = (k_1^* k_3^*) / (k_2^* + k_3^*)$ . Since K is the determining factor to LCMRGlc, where LC is a constant and  $c_p$  is measured by the blood sample, the determination of K can already provide a meaningful reference for clinical diagnosis. Therefore, although quantitative analysis of PET-FDG means the determination of LCMRGlc, only K is concerned in this study.

#### Input function model

##### A. Six-parameter PTAC model

Feng et al. proposed a PTAC model consisting of six parameters as follow [7]:

$$c_p^*(t) = [A_1 t - A_2 - A_3] e^{\lambda_1 t} + A_2 e^{\lambda_2 t} + A_3 e^{\lambda_3 t} \quad (4)$$

This model is the original model used in SIME method to generate the input function.

##### B. 1-point blood-sampling method by Wakita et al.

Wakita et al. examined and analyzed the input functions of 120 patients, and proposed a reference table [4]. In this method, only one venous blood sample is needed and it should be taken at the 40th minute after FDG injection. By applying this sample to the reference table for simple multiplication, a blood curve can be generated. To verify its correctness, the evaluation of this 1-point method is performed with the real sample at the 40th minute applied to this method. The results are satisfactory and prove that this method can provide a reliable input function model. In our study, this 1-point method is denoted as the 1-parameter PTAC model and used to replace the original six-parameter input function model in our method.

#### Conventional SIME method

In modeling theory, it is impossible to estimate simultaneously both the unknown input and system transfer function with only the output already known. However, if the initial guess for estimation and true parameters are close enough, the simultaneous estimation of the input and system

function might still be able to provide a reliable result. In addition, when more than one ROIs are chosen, the estimated

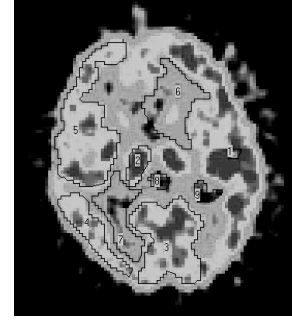


Fig.2 Locations of the nine ROIs circled in our study. The tenth ROI is of the whole brain.

input function will approach the true input function in theory. Based on this idea, SIME technique is proposed and simulated in [5] and further tested with three patient data in [8]. Its cost function is defined in [8] as:

$$\Phi(\theta) = \sum_{i=1}^N \sum_{j=1}^M [(\hat{c}_p^*(t) \otimes h_i(t)) \otimes \delta(t - t'_j) - c_{pi}^*(t'_j)]^2 + \sum_{k=1}^m w_k [\hat{c}_p^*(t_k) - \bar{c}_p^*(t_k)]^2 \quad (5)$$

where N is the total number of ROIs, M is the number of frames for each TTAC,  $h_i(t)$  is the impulse response function (IRF) of the  $i$ th ROI with microparameters  $k_1$ - $k_4$  and CBV,  $\theta$  denotes the vector of parameters to be estimated.  $\delta(t - t'_j)$  is a Dirac delta function shifted in time by units, and  $\otimes$  is convolution function.  $\hat{c}_p^*(t)$  is the estimated input function, and  $c_p^*(t)$  is FDG activity in plasma measured at time  $t_k$  ( $k=1,2,\dots,m$ ) [8].  $c_{pi}^*(t'_j)$  is the FDG activity in brain at time  $t'_j$ . The second summation term in this cost function is used for weighting in blood samples assumed in original procedure. Since this paper focuses on non-sampling techniques, this summation term can be cancelled, and the cost function is used in this study as:

$$\Phi(\theta) = \sum_{i=1}^N \sum_{j=1}^M [(\hat{c}_p^*(t) \otimes h_i(t)) \otimes \delta(t - t'_j) - c_{pi}^*(t'_j)]^2 \quad (6)$$

In the evaluation of this method, the initial guess of PTAC model are given as:  $A_1=851.1225$ ,  $A_2=20.8113$ ,  $A_3=21.8798$  (Bq/ml),  $\lambda_1=-4.1339$ ,  $\lambda_2=-0.1191$ ,  $\lambda_3=-0.0104$  (1/min). In our study, SIME uses three ROIs with one on gray matter (no.1 in Fig.1), one on white matter (no.6 in Fig.1) and one of whole brain, and the initial guess of  $h_i(t)$  are given as  $k_1 \sim k_4 = 0.1258, 0.2971, 0.0669, 0.0037$  for the gray matter,  $0.0553, 0.2429, 0.0668, 0.0092$  for white matter and  $0.0845, 0.2957, 0.0648, 0.0073$  for whole brain, and the CBV initial guess is 0.058.

#### Simplified SIME method

A new technique based on SIME method and the 1-parameter input function model is proposed in this paper. This method replaces the 6-parameter PTAC model in the SIME method with the 1-parameter model for generating input function, i.e.  $\hat{c}_p^*(t)$  is generated by only one parameter, the FDG activity in plasma at the 40th minute. In this paper, this new technique is denoted as SSIME (Simplified

Simultaneous Estimation). The main advantage of SSIME is the reduction of number of parameters for estimation. For example, if three ROIs are used in SIME, 21 parameters including 6 of the PTAC model and 15 of the IRFs have to be estimated simultaneously. However, only 13 parameters have to be estimated in SSIME method with 3 ROIs (In SSIME, CBV is not concerned in the IRFs). By reducing the number of parameters, not only the computation can be faster, but also the parameters can be adjusted with a wide range. Therefore, a more reliable recovered input function could be obtained by SSIME. In this study, SSIME with one, two, three and four ROIs are tested respectively. The initial guess of the ROI IRF is the same as mentioned in SIME method, and the initial guess of the single parameter of input function model is 249.5 (nCi/ml). The ROIs used in SSIME are (1) a ROI on gray matter (no.1 in Fig.2) for 1-ROI SSIME, (2) two ROIs with one on gray matter (no.1 in Fig.2) and one on white matter (no.6 in Fig.2) for 2-ROI SSIME, (3) three ROIs with one on gray matter (no.1 in Fig.2), one on white matter (no.6 in Fig.2) and one of whole brain in 3-ROI SSIME and (4) four ROIs with the same ROIs as 3-ROI SSIME, and plus another ROI on gray matter. (no.5 in Fig.2).

#### Data Analysis

In order to compare if the recovered PTAC is acceptable, two ways of data analysis are applied in this study. First, the recovered input functions are directly compared to the real input function from blood samples. The mean square error is defined as:

$$MSE = \frac{\sum_{i=1}^m [c_p^*(t_i) - \hat{c}_p^*(t_i)]^2}{m} \quad (7)$$

where  $t_i$  denotes time at  $m$  minutes after injection, and  $m=120$  in our study.  $c_p^*$  is the real input function and  $\hat{c}_p^*$  is the estimated input function. Since there are three methods mentioned in this paper, the DSE between the real input function and estimated input function by 1-point blood-sampling method by Wakita et al., SIME, and SSIME can be calculated respectively. One point to remember is that the emphasis should be put on the comparison of SIME and SSIME methods, because 1-point blood-sampling method requires one real blood sample and mismatches our goal of non-sampling schedule.

Second, since the estimated input function is used for the parameter estimation of  $k$  constants in FDG kinetic model, an estimated input function will only be “good” when it will provide as close result of  $k$  constants estimation as the real input function. To simplify this evaluation, only result of  $K$  is listed and compared in this paper, since  $K$  is the dominating factor of LCMRGlc as mentioned earlier. For each patient, ten ROIs are circled as shown in Fig.2 and their  $K$  constants are calculated via the real PTAC, PTAC estimated by SIME and PTAC estimated by SSIME to evaluate the  $K$  estimation performed to examine which method can provide a more correct  $K$  estimation result, with the calculation of correlation coefficient  $r$  and the regression equation. Finally, to compare the speed of each method, time needed for estimation process of each patient by MATLAB was also recorded.

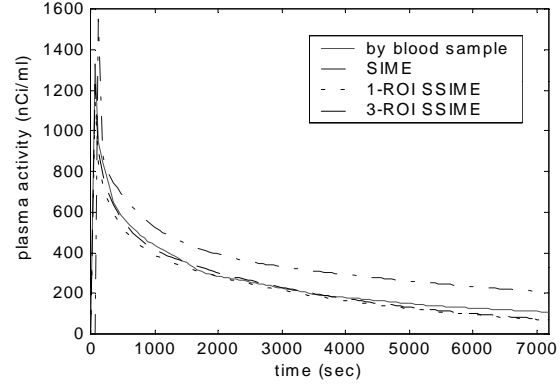


Fig. 3. The representative results of input functions from one subject. Solid line represents the real input function from blood samples. The figure shows the difference between SIME and SSIME, and the similarity of input functions from 1-ROI and 3-ROI SSIME methods.

### III. RESULTS

The overall comparison of the above three methods, including 1-point blood sampling method (by Wakita et al.), SIME and SSIME methods, was summarized in Table 1. Table 1 also included the results of SSIME with different number of ROIs. To evaluate the effect of location with the 1-ROI SSIME method, testing results were listed in Table 2, and Table 3 showed the effect of initial guess for input function. The representative estimation results of the input functions from SIME and SSIME were shown in Fig.3.

### IV. DISCUSSION

From the results of our experiment listed in Table 1, it can be found that SSIME can provide a closer recovered input function to the real one than SIME. As for the influence of  $K$  constant estimation, SSIME has a high correlation coefficient (0.93-0.941) and the slope of regression equation close to one (0.987-0.997). It is clear that SSIME will provide a more reliable result of  $K$  estimation than SIME. SSIME also has a faster speed for estimating input function. It takes only less than three seconds for 1-ROI SSIME and 25 seconds for 3-ROI SSIME to estimate the input function for a patient, while 3-ROI SIME takes about 37 seconds. In summary, the advantage of reducing total amount of parameters by SSIME can be observed clearly in the performance of speed and recovery ability.

From the results of Table 1, it is quite interesting that 1-ROI, 2-ROI, 3-ROI and 4-ROI SSIME methods seem to provide similar results. Especially in correlation coefficient and slope of regression equation of  $K$  estimation, 1-ROI SSIME provides the most reliable recovered input function in our experiment. The effect of using different ROIs in 1-ROI SSIME was tested by the use of ROI no.1, 2, 5, 6, 9 and 10 in Fig.2 respectively. Although ROI no.1 seems to be the most appropriate choice for 1-ROI SSIME, using a different ROI can still provide a fairly reliable estimated input function.

As mentioned earlier in this paper, one important factor to simultaneous estimation of input function and IRFs of ROIs is a “good” initial guess of these parameters, where “good”

means as close as possible. To evaluate the difference caused by different initial guess of input function parameter, 198, 249.5 and 302 were tested as initial guess in input function for 1-ROI SSIME as listed in Table □. From the correlation coefficient and regression equation, 249.5 is the most appropriate initial guess among three. For the much lower initial guess of 198, the correlation coefficient is reduced to 0.916, and slope of regression equation (1.23) shows that the estimated input function would cause an over-estimation effect of K constant estimation result. On the other hand, a much higher initial guess of 302 also reduces the correlation coefficient to 0.908 and the slope of regression equation is reduced to 0.86, which means the estimated input function would cause an under-estimation effect of K estimation result. In this paper, initial guess of the input function is suggested as 249.5 (nCi/ml) by analyzing our eighteen subjects. If more patient data could be collected and analyzed in the future, an optimal initial guess would be proposed in a more reliable statistical view.

In brief, the method suggested in this paper for estimating input function without any blood sample is the 1-ROI SSIME, with the ROI located on gray matter. The initial guess of the parameters is 249.5 for input function and  $k_1 \sim k_4 = 0.1258, 0.2971, 0.0669, 0.0037$  for the ROI-IRF.

TABLE □  
SUMMARY OF THE COMPARISON OF THREE DIFFERENT  
METHODS IN THIS PAPER

method	r	regression equation	MSE	time (sec)
1-point Wakita	0.965	$y = 0.9145x + 0.0004$	12104.4	0.00
SIME	0.854	$y = 0.9519x + 0.0022$	15628.8	36.87
1-ROI SSIME	0.941	$y = 0.997x + 0.0001$	10954.8	2.88
2-ROI SSIME	0.922	$y = 0.9958x + 0.0001$	10104.0	8.83
3-ROI SSIME	0.937	$y = 0.9836x + 0.0001$	10494.0	15.66
4-ROI SSIME	0.930	$y = 0.9871x + 0.0003$	10957.2	25.00

TABLE □  
SUMMARY OF THE ROI CHOICE COMPARISON IN 1-ROI SSIME

ROI choice	r	regression equation
ROI no.1	0.941	$y = 0.997x + 0.0001$
ROI no.2	0.924	$y = 0.9948x + 0.0005$
ROI no.5	0.922	$y = 1.022x + 0.0003$
ROI no.6	0.932	$y = 0.97x + 0.0002$
ROI no.9	0.925	$y = 1.0295x - 0.0005$
ROI no.10	0.928	$y = 0.9623x + 0.0002$

TABLE □  
SUMMARY OF COMPARISON OF INITIAL GUESS GIVEN TO INPUT  
FUNCTION IN SSIME

initial guess	r	regression equation
198	0.916	$y = 1.2332x - 0.0006$
249.5	0.941	$y = 0.997x + 0.0001$
302	0.908	$y = 0.8666x + 0.0002$

## V. CONCLUSION

We have proposed a reliable technique SSIME to estimate the input function without any blood sample. The results show that SSIME can provide good estimation of the input function with better efficiency and reliable estimation of K constants. This method can be applied in clinical diagnosis, and further investigation of error effect caused by the estimated input function should be undertaken in the future.

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